effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Glycol salicylate is also known as glycol monosalicylate, monoglycol salicylate, ethylene glycol monosalicylate, and 2-hydroxyethyl salicylate. It is the mono ester of ethylene glycol. It is prepared synthetically by esterification of ethylene glycol with salicylic acid. Its chemical nature and pharmacologic activities appear to be similar to methyl salicylate. It is a colorless, odorless liquid that boils at 169° to 172° C. One part of glycol salicylate is soluble in 110 parts water and in 8 parts olive oil. It is very soluble in alcohol, benzene, chloroform, and ether (Ref. 1).

(1) Safety. Clinical use has confirmed that glycol salicylate is safe in the dosage range used as an OTC external analgesic. In full strength concentrations, it has an irritant effect on the skin. Toxicity from oral ingestion is alleged to be due to the release of salicylate in the bowel and the absorption of the salicylate into the bloodstream. The symptoms are similar to those induced by other esters of salicylic acid.

Glycol salicylate is an ester of ethylene glycol.

Absorption of the drug through the skin or after oral ingestion may result in hydrolysis of the ester to ethylene glycol and salicylic acid. Ethylene glycol is oxidized to oxalic acid in the body. Oxalic acid is toxic if excessive quantities form. The Panel has no proof that this occurs with this ingredient when applied topically but feels this should be a point of interest in considering safety.

(2) Effectiveness. Glycol salicylate possesses no significant topical anesthetic activity and does not block the neuronal membranes as do the topical anesthetics, such as benzocaine, butamben, etc. It lacks sufficient counterirritant activity to be classified as a counterirritant. Although some degree of percutaneous absorption of salicylate esters occurs through the intact skin, no significant topical analgesic or anesthetic activity can be demonstrated. The Panel has insufficient evidence to classify glycol salicylate as a counterirritant.

It is claimed that glycol salicylate exerts its effect topically to relieve pain in muscles and structures beneath the skin by acting as an anti-inflammatory agent, as do other salicylates. Glycol salicylate does not act

as a counterirritant in the dosage form described below. Salicylate blood levels have been demonstrated after topical application in animals, but these have not been correlated with those occurring after oral ingestion of salicylate analgesics. Excretion of salicylates or metabolites has been demonstrated in the urine, but this is not proof of effectiveness. Claims are made that localized areas of myalgia and other painful musculo-skeletal disorders are relieved by the application of esters of salicylic acid to the affected part. The Panel concludes from available data that this action, if indeed analgesia results, is due to a systemic effect, and any analgesic effect is due to the blood-borne drug.

No evidence that relief of pain is due to a counter-irritating effect of the drug has been submitted from controlled studies. It is employed at concentrations of 1.9, 1.93, and 10 percent in combination products. In these combinations, counterirritants are included in the formulation. Data from controlled studies demonstrating the analgesic effect claimed has not been available.

The exact mechanism by which salicylates produce their analgesic effects is not known, but it is generally conceded that they act in part centrally, and in part by

exerting an anti-inflammatory effect peripherally, as does aspirin, by inhibiting prostaglandin synthesis. (See part III. paragraph B.3.a. above--Aspirin.) It is possible that the salicylate activity of glycol salicylate may also be due to an inhibitory effect on prostaglandin synthesis. There is no evidence that cutaneous analgesia or anesthesia results.

The Panel does not give serious consideration to the claim that glycol salicylate penetrates the skin and passes directly into the affected deeper structures to exert its analgesic effect. Although 8 to 10 percent concentrations of glycol monosalicylate have been used clinically, there is insufficient evidence on the effectiveness of such concentrations.

(3) Proposed dosage--For adults and children 2 years of age and older: Apply an 8 to 10 percent concentration of glycol salicylate to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See

part III. paragraph B.1 above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 583, 1976.

h. Hexylresorcinol. The Panel concludes that hexylresorcinol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Hexylresorcinol, an aromatic alcohol, is a dihydroxybenzene with a normal hexyl group on position 4 and hydroxyl groups on positions 1 and 3 of the aromatic

nucleus. It is, therefore, classifiable as a phenol. It responds to certain specific chemical tests characteristic of phenols. Hexylresorcinol is prepared by condensing resorcinol with caproic acid in the presence of zinc chloride. The resulting intermediate product is reduced to hexylresorcinol (Refs. 1, 2, and 3).

Hexylresorcinol is a white or yellowish-white powder composed of needle-shaped crystals. It has a faint "fatty" odor and a sharp astringent taste. When placed on the tongue, the ingredient produces a sensation of numbness. Hexylresorcinol melts at between 62° and 67° C. It turns from a white to a brownish-pink tint on exposure to light and air due to oxidation to quinones. One g of hexylresorcinol dissolves in approximately 2,000 mL of water. It is freely soluble in alcohol, methanol, glycerine, ether, chloroform, benzene, and vegetable oils. For many years hexylresorcinol was considered official and was included in the "United States Pharmacopeia."

(1) Safety. Clinical use has confirmed that hexylresorcinol is safe in the dosage range used as an OTC external analgesic.

Because hexylresorcinol was extensively used as an

anthelmintic and administered orally in both adults and children, the Panel considers it to be safe for topical application to the skin (Ref. 4). The usual adult dose as an anthelmintic is 1 g as a single dose in a 24-hour period. For children, the usual dose is 0.1 g for each year of age up to 10 years. The drug is usually given orally after an overnight fast. The presence of food lessens the effectiveness of the drug. A saline purge is usually given the following morning to clear the bowel of dead worms. Treatment may be repeated after 3 days (Ref. 1). Hexylresorcinol has also been shown to have some antimicrobial effects. The drug has been used as a gargle and as a urinary antiseptic. Experiments by Leonard (Ref. 5) resulted in the use of hexylresorcinol as a urinary antiseptic. He found that hexylresorcinol at pH 6 to 6.4 in a 1:60,000 concentration killed microbes in the urine in 1 hour, and that at pH 7.6 to 8.2, a concentration of 1:18,000 was required for the same effect. Robbins (Ref. 6) observed that after oral administration of hexylresorcinol to man, 18 percent was eliminated in the urine in a conjugated form, and 64 percent was eliminated in the feces in an uncombined state.

Animal studies indicate a low degree of acute and

chronic toxicity. In rats, the oral minimum lethal dose of a suspension is 50 mg/kg. A suspension in 5 percent olive oil solution administered subcutaneously resulted in a minimum lethal dose of 750 to 1,000 mg/kg. A similar low degree of toxicity was found in guinea pigs, rabbits, cats, and dogs. In dogs, doses of 1 to 3 g produced no signs of toxicity. When the dogs were sacrificed, mild irritation of the stomach was noted 4 to 5 hours after ingestion of the drug. Lesions in the mucosa were superficial. If the animals were sacrificed 48 hours later, the lesions were not present. Oral administration in rats revealed no signs of toxicity when a dose of 12 mg/kg was given 6 times over an 8-hour period and was well tolerated (Ref. 7).

Pure hexylresorcinol is irritating to the respiratory tract and to the skin. A concentrated solution of hexylresorcinol in alcohol has vesicant properties. It lacks the irritancy and caustic properties of resorcinol and phenol. Use over a period of 40 years and extensive marketing experience indicate that hexylresorcinol possesses a low degree of sensitization.

(2) Effectiveness. The Panel finds that hexylresorcinol has been used as an analgesic, anesthetic,

and antipruritic on the skin to relieve pain due to sunburn. In one study (Ref. 7) 100 adults participated. Their ages ranged from 14 to 74 years. Fifty subjects were treated with 0.1 percent hexylresorcinol and 50 subjects were treated with another agent. All 50 subjects treated with 0.1 percent hexylresorcinol obtained relief from pain and discomfort due to sunburn. No other clinical studies are available for the use of hexylresorcinol on the skin. However, hexylresorcinol is a phenol, and the substitution of an aliphatic radical on the side chain of this phenol attenuates the caustic activity but allows the retention of its phenolic qualities, which include analgesic, anesthetic, and antipruritic activity. Therefore, it is the Panel's opinion that hexylresorcinol does have analgesic properties.

In the cornea of rabbits, hexylresorcinol solution, 0.1 percent, produces topical anesthesia lasting various periods of time up to 10 minutes or more depending on the concentration of the hexylresorcinol. Hexylresorcinol has been incorporated in lozenges for the relief of sore throat and other painful ailments of the oral cavity.

Adriani and DiLeo (Ref. 8) found that the application

of a commercial preparation consisting of a 1:1000 solution produced analgesia on the gums and at the tip of the tongue, after stimulation by an electric current, but did not completely abolish sensation. With the exception of this study, the Panel has not received other reports of controlled studies on the analgesic effect of hexylresorcinol on the intact or damaged skin.

The ingredient has been recommended as an antimicrobial agent for cuts, wounds, and burns, but judgment of its effectiveness for these conditions does not come under this Panel's purview.

The range between the minimum effective dosage and the maximum allowable dosage as an external analgesic on the skin has not been established with certainty. The Panel questions the dosage recommended in the labeling of products on the market, which is that the ingredient be used full strength (0.1 percent) or diluted with an equal part of water. Therefore the Panel recommends that the effectiveness of this dosage range be adequately tested. (See part III. paragraph C. below--Data Required for Evaluation.)

(3) Proposed dosage--For adults and children 2 years of age and older: Apply a 0.05 to 0.1 percent

concentration of hexylresorcinol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 582-583, 1973.

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(4) Brown, E. A., W. Krabek, and R. Skiffington, "A New Antiseptic Solution for Topical Application (Comparative In Vitro Studies)," New England Journal of Medicine, 234:468-472, 1946.

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(6) Robbins, B. H., "Quantitative Studies on the Absorption and Excretion of Certain Resorcinols and Cresols in Dogs and Man," Journal of Pharmacology, 52:54-60, 1934.

(7) OTC Volume 060138.

(8) Adriani, J. and J. DiLeo, "The Effectiveness of Hexylresorcinol as a Topical Analgesic on the Mucous Membranes of the Oral Cavity," Draft of unpublished paper, in OTC Volume 060150.

i. Salicylamide. The Panel concludes that salicylamide is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Salicylamide, the amide of salicylic acid, is 2-hydroxybenzamide. It is a white, crystalline, almost odorless powder. It is poorly soluble in water. One g dissolves in 500 mL water, 15 mL alcohol, 100 mL chloroform, and approximately 35 mL ether (Refs. 1 and 2).

(1) Safety. Clinical use has confirmed that salicylamide is safe in the dosage range used as an OTC

external analgesic.

Although salicylamide is the amide of salicylic acid and is generally discussed along with the salicylates as an analgesic, it is not converted to free salicylates in the body when the ingredient is ingested orally (Ref. 1). It is rapidly conjugated with glucuronic and sulfuric acids by enzymes in the mucosal wall of the intestines and the liver. The conjugates are excreted into the urine. Patients sensitive to aspirin apparently are not sensitive to salicylamide, because it is not converted to salicylic acid or any of its salts or esters. Its use topically is safe and it causes no irritation to the skin (Ref. 3).

Spickard (Ref. 3) reported no evidence of irritancy after application of a preparation containing 5 percent salicylamide and 1 percent benzocaine dissolved in isopropyl alcohol and polyoxyethylene lauryl ether to 237 subjects. Three drops were applied to the forearm every other day. Readings for any evidence of rash or irritation were made 24 hours after each application. After a series of 10 applications and a rest period of 10 days, a single repeat application was made and the effects of this application were noted 24 hours later. Seven subjects reacted with itching and redness after the first or subsequent applications. After the 10-day rest period,

only two individuals reacted. The two individuals would be considered to have shown an allergic reaction according to the Draize method.

Salicylamide is used orally as an analgesic; however, there is some question concerning its safety after oral ingestion. The oral lethal dose of salicylamide in man has not been established. A minimum of 1,000 mg administered orally every 4 hours must be used to obtain analgesia, but not more than 6,000 mg should be used in 24 hours. This dosage must not be used for more than 10 days (see the report of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products, published in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346)). Higher oral doses of salicylamide may produce drowsiness, dizziness, and gastrointestinal upset (Ref. 1). Another toxic manifestation in analgesic dosages is hepatic insufficiency in children. Damage to blood-forming elements following chronic use is sufficiently serious to warrant additional study. Whether sufficient quantities are absorbed through the skin to produce these effects is not known, but none of these adverse reactions has been brought to the attention of the Panel. Salicyl-

amide, in contrast to aspirin and other salicylates, has no effect on the clotting mechanism or platelet aggregation and does not affect bleeding time or clotting time. Allergic reactions to salicylamide are rare. Cross-sensitivity to aspirin does not occur.

(2) Effectiveness. Salicylamide or its metabolites can be detected in the urine when the drug is applied topically to the skin (Ref. 3). A submission to the Panel contained the following statement: "The determination of blood levels in rabbits and of the urinary excretion in humans and in rabbits of benzocaine and salicylamide had established that the active ingredients are absorbed through the intact skin. However, these experiments did not permit any direct conclusion concerning the possible penetration of these drugs into the muscle tissues." The Panel agrees with these statements in the submission. The following statement is also found in the submission: "By inference, such a penetration is indicated by the relief of pain following topical application." The Panel does not agree with this statement, however (Ref. 3).

Studies carried out in six rats revealed the presence of salicylamide in muscle tissue. The Panel does not

disagree that percutaneously absorbed drugs can be detected in tissue, because such drugs pass into the systemic circulation and are redistributed to various organs and tissues. However, the mere presence of the drugs in tissues does not necessarily mean that their effect is based there, unless the tissue concentration approaches that found in the plasma when these drugs are given orally and cause their effects. No data derived from controlled studies in man have been submitted to substantiate claims of pain relief in muscles and other structures beneath the skin. Evidence of pain relief in a double-blind, crossover type of study would be helpful in making a judgment.

Letters from users of the marketed preparation describing the relief of muscular aches and pains were submitted as evidence of the effects claimed in the labeling (Ref. 3). The Panel regards these reports as anecdotal and considers them to be testimonials not based on facts. Factual data to substantiate the claims made in the labeling have not been submitted.

When ingested orally, salicylamide is almost completely metabolized to pharmacologically inactive substances during its passage from the gastrointestinal

tract to the liver, before it is even absorbed into the systemic circulation to become available at the therapeutic site of action. This initial absorption before it becomes therapeutically effective in sufficient concentrations in the systemic circulation is sometimes referred to as the absorptive phase. In this absorptive phase, the salicylamide is metabolized by conjugation with glucuronic acid and sulfuric acid. The conjugates are excreted into the urine. The biotransformation at low oral doses is so extensive that little, if any, active unmetabolized drug is available for absorption into the systemic circulation for distribution to the sites of therapeutic action (see 42 FR 35346, July 8, 1977) (Ref. 4).

Because the drug is poorly water soluble, the Panel feels the amount available for absorption via the skin is limited. The bioavailability through the skin, therefore, is questionable. Evaluations of analgesic potency of salicylamide in animals indicate that a wide range of effectiveness exists and that there is considerable disparity between the results of different observers when the drug is compared to aspirin. In man, however, salicylamide has been shown to have little, if any, superiority over aspirin. Oral doses below 600 mg are not

effective and the analgesic effects are indistinguishable from the placebo. For two reasons the Panel doubts that quantities absorbed through the skin are effective, even when blood-borne. First, the substance is metabolized quickly, and second, its efficacy is questionable because the effect of 600 mg orally is indistinguishable from placebo. It is doubtful that 600 mg is absorbed by local application to the skin. Furthermore, salicylamide has no anti-inflammatory activity (see 42 FR 35346, July 8, 1977).

The Panel has had no evidence submitted to it that salicylamide possesses topical anesthetic activity and blocks neuronal membranes as do the topical anesthetics of the "caine" type, such as benzocaine, tetracaine, lidocaine, etc. There is no evidence that salicylamide possesses topical analgesic, anesthetic, or antipruritic activity for the relief of cutaneous disorders (Ref. 3).

There is no disagreement that some degree of percutaneous absorption of salicylic acid derivatives occurs through the intact skin (Ref. 5). Blood levels of salicylates have been demonstrated in animals. Claims are made that pain and discomfort resulting from myalgia and other musculoskeletal disorders are relieved by the

application of preparations containing derivatives whose effect is systemic and that any analgesic effect is due to the blood-borne drug. The Panel does not consider the quantity that would be absorbed by percutaneous routes to be sufficient to induce analgesia systemically as is the case with oral preparations. The exact mechanism by which derivatives of salicylic acid produce their analgesic action is not known, but it is generally conceded that they act not only centrally but also in part by exerting an anti-inflammatory effect. Not all derivatives of salicylic acid exert anti-inflammatory effects. Salicylamide does not have an anti-inflammatory effect. Therefore the Panel does not give serious consideration to the claim that the drug penetrates the skin and passes directly into the affected deeper structures to exert an analgesic effect (see 42 FR 35346, July 8, 1977).

Salicylamide has been used in a concentration of 35 percent with benzocaine.

(3) Proposed dosage--For adult and children 2 years of age and older: Apply a 3 to 10 percent concentration of salicylamide to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is

no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for external analgesics. (See part III. paragraph C. below--Data Required for Evaluation.)

REFERENCES

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1033, 1973.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1079, 1976.

(3) OTC Volume 060119.

(4) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan

Publishing Co., Inc., New York, p. 348, 1975.

(5) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co. Philadelphia, p. 1035, 1973.

j. Thymol. The Panel concludes that thymol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Thymol, also known as thyme camphor, is 5-methyl-2-isopropyl-1-phenol. It may be prepared synthetically or obtained from volatile oils distilled from Thymus vulgaris and other related plant sources. Thymol occurs as colorless crystals, which are often large, or as a white crystalline powder. It melts at 51° C and boils at 233° C. One g dissolves in 1 liter water. It is highly soluble in alcohol, chloroform, and in mineral oil and other fixed and volatile oils (Ref. 1). It has a characteristic aromatic thyme-like odor and a pungent

taste. Thymol has appreciable volatility in water vapor when it is prepared in aqueous solutions.

(1) Safety. Clinical use has confirmed that thymol is safe in the dosage range used as an OTC external analgesic.

Thymol has a pleasant aromatic odor. In the past, it has found its way into a wide variety of medicinal uses but has in many cases been superseded by other newer and more effective drugs. It has been incorporated into mouthwashes for its antiseptic action and has been used topically and orally for the treatment of actinomycosis. It has also been used internally as an intestinal antiseptic and anthelmintic, especially against hookworm (Refs. 2 and 3).

The LD_{50} in mice was found to be 74 mg/kg when thymol was injected intravenously (Ref. 4). Jenner (Ref. 5) studied the acute oral toxicity of thymol by intubation in the rat and guinea pig. The LD_{50} for the rat was found to be 980 mg/kg, and for the guinea pig, 880 mg/kg.

Chronic toxicity was observed in five male and four female rats given an oral dose of 10,000 parts per million for 19 weeks. No untoward effects were found (Ref. 6).

Ingestion of 1 g thymol usually does not cause any adverse symptoms other than a feeling of warmth generated in the stomach. Doses larger than 1 g have resulted in gastrointestinal irritation marked by dizziness, excitement, and severe epigastric pain, followed by vomiting, nausea, marked weakness, sweating, collapse, and slowed pulse and respiration. Abortion has also resulted (Ref. 3).

Worm infestations have been treated in the past with thymol, especially in the Far East. A report by Barnes noted that over a million doses of thymol averaging 1 g per dose resulted in reported deaths of 20 debilitated patients (Ref. 7).

Samitz and Shmunes noted that dentists and other allied personnel found thymol one of the less frequent sensitizers in occupational dermatoses (Ref. 8). Thymol irritates the mucous membranes, but has little effect when applied topically to the skin and is virtually unabsorbed (Ref. 3). The oral toxicity of thymol is about one-fourth that of phenol; if absorbed, half is metabolized totally, and the remainder is conjugated with sulfuric and glucuronic acids and excreted into the urine (Ref. 3).

(2) Effectiveness. Thymol was first introduced as a

disinfectant. It has a phenol coefficient of 27.6, but its activity is greatly reduced in the presence of proteins. It also has some antiviral activity (Ref. 9). Potter, in 1891 (Ref. 10), stated that thymol was a topical anesthetic for use on the skin and mucous membranes. Buckley (Ref. 11) also noted that thymol had topical analgesic properties and considered it superior to phenol as an antiseptic.

Thymol has been referred to another Panel for the determination of its safety and efficacy as an antimicrobial and antifungal agent.

The Panel concedes it is possible that thymol is a topical analgesic, anesthetic, and antipruritic because of its phenolic nature, but the Panel does not have sufficient evidence and documentation to support this claim. Most of the literature refers to the antimicrobial and antifungal effects of thymol. Although 1 to 2 percent concentrations of thymol have been used clinically for topical analgesia and anesthesia, there is insufficient evidence of the effectiveness of such concentrations.

(3) Proposed dosage--For adults and children 2 years of age and older: Apply a 1 to 2 percent concentration of

thymol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below--Data Required for Evaluation.)

REFERENCES

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(2) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1101, 1975.

(3) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227-228, 1957.

(4) Edwards, E. H. and B. Hall, "Thymol as a Bacteriostatic Agent," The Pharmaceutical Journal, 166:54, 1951.

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(6) Hagan, E. C., W. H. Hansen, O. G. Fitzhugh, P. M. Jenner, W. I. Jones, J. M. Taylor, E. L. Long, A. A. Nelson, and J. B. Brouwer, "Food Flavorings and Compounds of Related Structure. II. Subacute and Chronic Toxicity," Food and Cosmetics Toxicology, 5:141-157, 1967.

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(9) Dunham, W. B. and W. J. MacNeal, "Culture on the Chick Chorioallantosis as a Test of Inactivation of Coccinea Virus," Journal of Bacteriology, 44:413-424, 1942.

(10) Potter, S., "Handbook of Materia Medica Pharmacology and Therapeutics," 3d Ed., Blakiston Press, Philadelphia, p. 389, 1891.

(11) Buckley, J. P., "Modern Dental Materia Medica Pharmacology and Therapeutics," 5th Ed., W. B. Saunders Co., Philadelphia, pp. 48, 50, and 515, 1926.

k. Triethanolamine salicylate. The Panel concludes that triethanolamine salicylate is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Triethanolamine salicylate is an ester produced by the interaction of equal amounts of triethanolamine and salicylic acid. Triethanolamine salicylate is a light reddish, viscous liquid with a faint odor and a specific gravity of 1.280 to 1.980. Triethanolamine salicylate is miscible in all proportions with water, glycerine, propylene glycol, isopropyl alcohol, and 95 percent ethyl alcohol. It is insoluble in mineral oil and vegetable oils.

(1) Safety. Clinical use has confirmed that triethanolamine salicylate is safe in the dosage range used as an OTC external analgesic.

The oral LD_{50} of triethanolamine salicylate in rats is 2.8 g/kg. Animal and human toxicological data indicate that it is safe for topical application. Its average

Draize primary skin irritation index is 1.5. Triethanolamine salicylate is not a topical irritant and has minimal sensitizing potential (Refs. 1, 2, and 3). An intracutaneous sensitization test in 10 guinea pigs over 5 weeks revealed no sensitization reactions on repetitive examinations. Repeated insult patch tests of the lotion formulation, using the Draize human skin irritancy test in 52 women and 5 men gave the following results: After 9 applications to the upper arm in 21 days and a challenge at 35 days, there was revealed a slight erythema at the application sites in 4 individuals. This is presumptive evidence that triethanolamine salicylate is not a sensitizer (Ref. 2).

(2) Effectiveness. Triethanolamine salicylate, which penetrates the intact and damaged skin, does not block the neuronal membranes as do the topical anesthetics, such as benzocaine, etc., and therefore possesses no topical anesthetic activity. Some degree of percutaneous absorption of salicylic esters occurs through the intact skin (Refs. 4, 5, and 6), but no significant analgesic or anesthetic activity has been demonstrated. Blood levels have been demonstrated following topical application with various techniques in animals. These blood levels have

not been correlated to blood levels of salicylate-type analgesic ingredients administered by the oral route. Triethanolamine salicylate is not a counterirritant analgesic salicylate ester.

In the absence of such comparative data, the Panel does not give serious consideration to claims made for the effectiveness of triethanolamine salicylate as an analgesic for muscle aches and pains because it is doubtful that sufficient quantities are absorbed from the skin to be blood-borne. Gaudin (Ref. 7) noted that approximately 15 percent of a topically applied amount of triethanolamine salicylate on rabbit skin appeared in the urine as salicylic acid and that 9.46 percent sodium salicylate was found in the urine by comparison (Ref. 1). The Panel does not disagree that salicylates are absorbed from the skin, but it does not agree that this is proof of effectiveness of these drugs as analgesics on the structures beneath the skin to which they are applied. Excretion of salicylates or metabolites into the urine has been demonstrated (Ref. 1).

Claims have been made that localized areas of myalgia and other painful musculoskeletal disorders are relieved by the application of esters of salicylic acid to the

affected part. The Panel concludes from available data that this action most likely is systemic and any analgesic effect is due to the blood-borne drug. The Panel does not believe that evidence has been provided to indicate that sufficient quantities are absorbed to induce analgesia. The exact mechanism by which salicylates produce their analgesic effect is not known, but it is generally conceded that they act in part centrally, and in part peripherally, by exerting an anti-inflammatory effect by inhibiting the synthesis of protaglandins. (See part III. paragraph B.3.a. above--Aspirin.)

Some evidence exists that salicylates inhibit the synthesis of prostaglandins and relieve pain in this manner. References cited in the submission for effectiveness of the ingredient refer to salicylates but provide no data concerning triethanolamine salicylate (Refs. 1 and 3). The only proof of efficacy is that salicylates are absorbed percutaneously (Ref. 8).

The Panel does not give serious consideration to the claim that the drug penetrates the skin and passes directly into the affected deeper structures in sufficient concentration to be effective because there is no data to substantiate this claim (Refs. 1 and 3).

Triethanolamine salicylate has been used topically in concentrations of 5 to 10 percent, but there are no data available to substantiate its effectiveness in that dosage range.

(3) Proposed dosage--For adults and children 2 years of age and older: Apply a 5 to 10 percent concentration of triethanolamine salicylate to affected area 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above--Category I Labeling.)

(5) Evaluation. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for external analgesics. (See part III. paragraph C. below--Data Required for Evaluation.)

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(3) OTC Volume 060144.

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(5) Todd, R. G., "Martindale, The Extra Pharmacopeia," 25th Ed., The Pharmaceutical Press, London, p. 26, 1967.

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(7) Gaudin, O., "Amine Salicylate Ointment," U. S. Patent: 2, 596, 674, May 13, 1952.

(8) Plein, J. B. and E. M. Plein, "A Comparison of In Vivo and In Vitro Tests for the Absorption, Penetration, and Diffusion of Some Medicinals from

Silicone and Petrolatum Ointment Bases," Journal of the American Pharmaceutical Association, 12:705-717, 1957.

Category III Labeling

The Panel concludes that there are insufficient data available at this time to permit final classification of the following claims:

Claims for relief of deep-seated pain. The Panel finds that there is insufficient evidence that external analgesic ingredients penetrate beneath the skin to relieve deep-seated pain. Claims such as "penetrates deep into the skin and relieves pain arising from deep down inside," "penetrating heat relief," and "deep strength" are unsubstantiated and require further testing. The Panel has classified such claims as Category III.

C. Data Required for Evaluation.

The Panel considers that the protocols recommended in this document for the studies required to bring Category III external analgesic ingredients into Category I reflect the present state of the sciences of pharmacology and toxicology. The protocols do not preclude the use of newer or more refined laboratory or clinical investigative methods to establish safety or effectiveness of an ingredient. Manufacturers are expected to furnish only data relevant to unanswered questions regarding the safety and efficacy of the ingredients in their product. They are not expected to furnish all the data listed in the guidelines below.

Safety studies are required if the data submitted to date have not substantiated claims that an ingredient is safe when applied externally on the intact or damaged skin. Efficacy studies are required if the data submitted to date have not substantiated the claim that an ingredient is effective.

1. General considerations. a. Pain is a subjective sensation in response to noxious stimuli. Lack of reactivity when noxious stimuli are applied without production of pain indicates that a state of analgesia has been induced. The appraisal of the analgesic activity of an

ingredient or a combination of ingredients must be based upon their ability to relieve pain caused by a disease process or trauma. The pain experience in man consists of perception of painful stimuli, together with the psychologic modification of the response to these stimuli. Animal screening tests and methods using experimentally induced pain in normal human volunteer subjects generally do not yield consistent results nor are the results in humans similar to those obtained in studies of pain of pathologic origin (Ref. 1). The only exceptions the Panel considers applicable are pain due to burns of the skin induced by ultraviolet radiation and pain due to experimentally produced abrasions or excoriations. Skin pain is localized. Experimentally induced pain from ultraviolet light burns is generally the same type as pathologically induced sunburn pain, and pain due to abrasions in volunteers is similar to that caused accidentally by trauma to patients. Objective methods for studying pain in humans, either experimentally produced pain or pathologic pain, are not available. The efficacy of analgesic drugs, both in laboratory and clinical situations, must be appraised by accepting the subject's own reports on indices of pain experiences and the relief

obtained by topical administration of external analgesics.

b. Certain general comments pertaining to the preparation of protocols in the evaluation applicable to all external analgesic ingredients considered by the Panel (analgesics, anesthetics, antipruritics, and counterirritants) are discussed below. Comments applicable only to analgesics, anesthetics, and antipruritics and those pertaining only to counterirritants are also considered below in separate discussions.

The Panel concludes it is reasonable to allow 3 years for the development and review of evidence that will permit final classification of the effectiveness of the Category III ingredients aspirin, glycol salicylate, salicylamide, triethanolamine salicylate, and thymol, and for the indication for deep-seated pain. The Panel concludes that it is reasonable to allow 2 years for the development of data for all other Category III conditions. The ingredients pose no serious problem for the consumer. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 or 3 years as specified, the ingredients should no longer be marketed in OTC products.

2. Procedure for conducting studies on normal volunteer subjects and patient. Investigational studies of a proper design should be conducted on human volunteers if reproduction of a particular skin condition is feasible (Ref. 2). Examples of experimental designs that may be appropriate include crossover, double-blind, factorial, sequential trial, single-blind trial, and therapeutic equivalency. Preference should be given to a double-blind study with controls, so that it will demonstrate the efficacy of the product. The cross-over technique should be used, if possible. When that technique is used, a period of 12 hours or more should be allowed to eliminate all of an absorbed drug from the system. If the identity of an ingredient cannot be masked when a double-blind study is performed, and if a suitable placebo is not available, control and treatment periods should be of sufficient duration to allow subjects to serve as their own control. The number of subjects used in such a study should be sufficient to permit statistical analysis of the data obtained (Ref. 2). The number tested should be sufficient to eliminate examiner bias, bias due to placebo effect, and the effects of psychological responses to pain in tested subjects. The subjects should be of both sexes

and within the age groups for which use of the product is intended. The subjects should be healthy and free from any ailment and should not be receiving any oral, parenteral, or topical medication. Female subjects should not be pregnant. The study should be of sufficient duration to demonstrate efficacy. The treatments should be selected on a random basis. The number and frequency of the applications of the preparation should be the same as would be the case for clinical use. Any manifestation of local or systemic irritancy, sensitivity, or toxicity in these tests should be recorded.

When studies are performed in clinical situations, a large number of appropriate subjects with different types of pain should be studied. Differentiation of patients should be made in accordance with the type of pain, i.e., pain due to inflammation, burns, or that arising in joints, muscle, etc. The randomization procedure should be made so that variables not otherwise controlled balance out.

There should be detailed explanation of the criteria for assessment of the condition to be treated by the ingredient, of the method employed in testing, and of the validity of the method or methods used. A medical

history, demographic data, and physical data including physical examination, laboratory studies, and other pertinent data should be obtained and recorded for each subject.

Studies should be performed on patients who have lesions, pain, burns, etc. Subjects who have similar kinds of conditions and are being treated with a preparation should be divided into a treated group and a "placebo" group to obtain a controlled study. Again, "before treatment" data should be obtained and recorded. The degree of relief of symptoms, the onset of action, whether partial or complete, the duration of action, and the presence or absence of any rebound after the analgesic effect wears off should be noted. A grading or scoring technique should be used to determine degree of relief. The application of the medicament should be in accordance with the method outlined below and the indication for use on the labeling. The tests should be performed using the final product formulation.

The range between the minimum effective concentrations and the maximal allowable (safe) concentration should be supplied when lacking. This may be expressed as a percent concentration of the preparation. Consideration should be given to how the drug is absorbed or penetrates the skin, its duration of action, and its relationship to the length of time it remains on the skin. In cases where claims are made that a drug penetrates the skin and passes directly into deeper structures such as muscles and joints and causes relief of pain, such direct penetration and pain relief must be shown to occur. The mere fact that the drug is absorbed and is detectable in the blood, or is excreted into the urine in its pure form or as metabolites, will not be sufficient evidence of efficacy.

An attempt should be made to determine the possible mechanism of action or actions of the drug.

3. Interpretation of data. Records should be detailed and should include legends, with specific explanation of codes, doses, mode and time of application, the period of latency from the moment of application to the development of the desired therapeutic effect, the frequency of testing, and the duration of test period. Investigative methods should be described in detail so

that the experiments can be repeated to verify and confirm results obtained by the investigator (Ref. 2).

Provision should be made to eliminate examiner bias in either volunteer or clinical trials. Proper interpretation and explanation of the results should be provided. Whenever possible, statistical analysis should be employed to evaluate the results. Consideration should be given to the placebo effect of a drug.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

4. Safety evaluation. Adequate, acceptable controlled in vivo studies of acute and chronic toxicity in several species of animals should be supplied. The oral LD_{50} in animals should be established. The range of the toxic dose in humans should be made available if possible, because individuals, especially children, may accidentally ingest or inhale overdoses of these medications (Ref. 2). If the ingredient has been classified Category III for safety reasons, studies on chronic toxicity should be performed by two independent investigators over a 3-month

period.

Tests should be performed for acute eye irritancy, primary skin irritancy, corrosivity, acute dermal toxicity, and subacute dermal toxicity in animals (rabbits). Tests for topical irritancy and topical and systemic sensitivity in man should be performed if such data are not available. Acceptable methods for testing for irritancy and sensitivity are described by Kligman and by Shelanski and Shelanski (Refs. 3 and 4).

Data on systemic absorption, distribution, metabolic fate, half-life, rate of excretion, and possible cumulative effects should be supplied wherever indicated in the ingredient statements discussed elsewhere in this document. (See part III. paragraph B.3. above-- Category III active ingredient.)

a. Recommended toxicological studies. The Panel used data on "complaints per unit sold" submitted by the various companies as one of the criteria for evaluating human safety of ingredients and combination products. However, anecdotal descriptions of toxicity were not given serious consideration.

A variety of toxicological methods may be used to obtain data substantiating that a preparation is safe.

Manufacturers are expected to conduct studies using the first five methods listed below. Methods 6 through 8 may be used to augment and confirm data obtained using methods 1 through 5. The Panel recognizes that better testing methods may be developed in the future. The requirements listed below will not preclude use of such methods in the event that they become available.

b. Preclinical animal studies.

(1) Acute oral LD_{50} toxicity in rats.

(2) Acute eye irritation in rabbits.

(3) Primary skin irritation and corrosivity in rabbits.

(4) Acute dermal toxicity in rabbits.

(5) Phototoxicity and photosensitization studies.

(6) Acute toxicity of inhaled aerosols and sprays in rats.

(7) Subacute dermal (21-day) toxicity in rabbits.

(8) Skin sensitization in rabbits or other suitable test animals.

c. Safety studies in man. A number of patch test methods have proven valuable in predicting skin irritancy and sensitization. These involve the use of occlusive dressings impregnated with the drug applied at various

time intervals to selected sites in the subject's skin, allowing rest periods for possible sensitization to develop. Responses occurring within several days are indicative of irritancy. These areas are then challenged with the test drug after rest periods to determine whether sensitization has occurred. The Panel recommends the use of one of the following methods (1) The Draize human skin irritancy and sensitization tests and its various modifications utilizing the subject's back or arm may be used (Ref. 5).

(2) The method of Shelanski and Shelanski (Ref. 4) is one in which the active ingredient or formulation is applied regularly to the test site for 3 to 4 weeks. Then, following a rest period of 2 weeks, there is a single challenge application of the drug or formulation (Ref. 4). The early applications are to detect primary skin irritants and initiate sensitization in susceptible persons. The challenge dose is to detect skin sensitizers.

(3) The maximization procedure of Kligman or its modifications uses an irritant on the test site, thereby hastening and accentuating the skin-sensitizing potential of a substance (Ref. 3).

The effectiveness of certain ingredients can be correlated with the degree of percutaneous absorption, which may also be correlated with systemic and local toxicity. Studies on penetration of drugs through the skin of animals unfortunately cannot be extrapolated to man. Some drugs are absorbed in excessive quantities if applied to large surface areas of the body. The degree of absorption or penetration may be determined by studying blood levels and measuring the total quantity excreted. Inferences of safety may be based on the observed drug levels and their correlation with toxicity studies.

The Panel considers certain in vitro studies applicable for establishing criteria for safety and effectiveness. The method of Fritsch and Stoughton is an example of an in vitro method in which excised human skin is used for studies on penetration (Ref. 6). Studies utilizing the friction blister, suction blister, sunburn blister, blister caused by freezing skin with liquid nitrogen, dermatome specimens, and excised skin are acceptable. Drug penetration through a blister top may be determined by analyzing the blister fluid. In addition, the top of the blister may be excised and analyzed quantitatively for the drug to determine the degree of

absorption into the skin layers.

Topical anesthetics, topical analgesics and topical antipruritics, once through the epithelial barrier, pass into the tissue fluids beneath, into the venules and lymphatics and are distributed to various tissues, particularly those that are capillary rich. Some esters of topical anesthetics, such as tetracaine, are hydrolyzed by plasma esterases into the alcohol and acid from which they were formed, and are thereby inactivated. The amide type of topical anesthetic is not altered by esterases but ultimately passes from the blood and tissues to the liver, where it undergoes biodegradation (detoxification). The byproducts are eliminated into the urine. Topical anesthetics that are not hydrolyzed by plasma esterases or easily detoxified by the liver, such as dibucaine or cocaine, are eliminated unchanged by the kidney. Alcohol-type topical anesthetics are not affected by the plasma esterases. They are detoxified by the liver through various types of chemical reactions, such as oxidation, reduction, conjugation, or transfer reactions. Unmetabolized portions are excreted into the urine.

Solvents and other substances used to formulate a finished product that penetrates the barriers are

detoxified in the same manner as the active ingredients. It is possible for highly lipophilic substances that are used daily for long periods of time to accumulate in the adipose and other lipid-rich tissues, particularly if they are not readily biodegradable, where they may remain for days, weeks, or months (Refs. 7 and 8). None of the ingredients the Panel has evaluated is retained for long periods of time in adipose or lipid-rich tissues. Methods to detect minute quantities of some substances are not available, and in general, no standard procedure to measure skin penetration in humans exists. Animal studies should be performed as a preliminary to human in vivo testing (Ref. 2).

NOTE: The above considerations pertain to all external analgesics. The following two sections deal with methods of evaluating analgesics, anesthetics, and antipruritics, on the one hand, and counterirritants, on the other.

5. Evaluation of analgesics, anesthetics, and antipruritics. Anesthetics, analgesics, and antipruritics produce their effects by depressing cutaneous sensory receptors or by the removal of noxious stimuli that induce pain. Corroborating data for many ingredients and prepa-

rations evaluated by the Panel can be obtained by inducing pain experimentally in normal volunteers. Methods for inducing experimental pain are described below, as are methods for measuring the intensity of pain. Some of these methods are suitable for determining effectiveness of analgesic ingredients on both the intact skin and damaged skin. Data obtained using these ingredients to relieve experimentally induced pain are acceptable as corroborating evidence only, but data from clinical studies must be submitted in support of an evaluation. Although the general comments outlined above for preparation of protocols are applicable to this group of ingredients, certain modifications or additional comments are necessary in obtaining data for evaluation of anesthetics, analgesics, and antipruritics.

a. Mode of application. The Panel emphasizes that the mode of application of the ingredient under study is an important consideration and should be specified in the evaluation report. Some preparations are merely applied, without rubbing or massaging, in the form of a film on the intact skin or over a lesion where the skin is not intact. Rubbing and massaging may accelerate the absorption as much as 24 to 50 percent (Ref. 9).

The frequency of application should be recorded. Data obtained following a single application cannot be used to substantiate claims made when a preparation is intended for multiple applications.

b. Studies on the damaged or abraded skin. The Panel stresses that there is considerable difference between studies performed on intact skin and those performed on skin that has been damaged as a result of injury, trauma, disease, or other causes. When an ingredient is applied to the abraded skin, the avenues of access for an active ingredient to subepidermal structures are open and absorption occurs readily. Contact, therefore, is readily made with the terminal receptors that subserve pain and itch and other sensations. If the agent is of sufficient potency, anesthesia may result.

The minimum effective concentration on the damaged abraded skin is less than it is on the intact skin. The "horny layer" or dermis provides an effective barrier, through which drugs, chemicals, or noxious agents are not able to penetrate unless they are of a lipophilic nature (Refs. 9 and 10). The stratum corneum, the outer horny layer of the epidermis, is made of dead, keratinized cells that have lost their nuclei in the process of keratini-

zation. They maintain their physiologic connection with neighboring cells through bridges called desmosomes. This layer of keratin acts as a barrier and protects humans from the environment (Ref. 9).

The stratum corneum is strongly hydrophilic. The amount of water in this layer depends mostly on the moisture content of the environment and partly on the water supply available from the body itself. This water-holding capacity of keratin confers upon the skin its property of suppleness (Ref. 9). Substances soluble in both water and lipids readily and easily pass through this layer. Damage to, or removal of, the stratum corneum allows practically any molecule, regardless of size, to pass through the skin (Ref. 9). Meaningful data can be obtained by abrading the skin of normal volunteers and studying the effect of topical analgesics, anesthetics, and antipruritics on these areas. The techniques that can be used are described below.

c. Evaluation of analgesic and antipruritic agents exerting anti-inflammatory effects. The Panel also recognizes that the methods described below may not be suitable for evaluating the effectiveness of analgesic and antipruritic drugs that do not block nerve fibers and

prevent transmission of nerve impulses, such as the anti-inflammatory agents. The steroids, antihistamines, and other drugs are anti-inflammatory agents that act by reducing edema and alleviating pressure on cutaneous receptors that incite the sensation of pain. The Panel recommends in these instances that studies of these products be performed on patients with edema of the skin and inflammatory conditions using the protocol described above. (See part III. paragraph C.1. above--General considerations.)

d. Methods of studying salts of bases. Some active ingredients considered by the Panel are bases but are present in the formulation in the form of a salt, or the media in which they are incorporated are acidic and convert the bases to salts. The salts do not penetrate the intact skin because they are ionized and are not lipophilic (salts of lidocaine, tetracaine, dibucaine, etc.) (Ref. 10). In most instances, these salts have been placed in Category I for use on the damaged, excoriated, or abraded skin because they readily come into contact with the nerve endings in the tissues and are effective for relief of pain and itching on the skin.

It is the opinion of the Panel that these ingredients

that are active as bases on the intact skin, but are not active as salts, could be buffered or neutralized and converted to bases. The finished product could be reformulated to contain the concentration of the ingredient that is effective. The salt may be effective at a higher concentration than is present in the formulation, in which case the concentration may have to be increased to the effective level. In either case, efficacy and safety studies that meet the criteria in the above guidelines should be conducted. The concentration of active ingredients that are present in less than the minimum concentration considered to be effective by the Panel should be increased to the minimum effective concentration in the formulation (Ref. 10).

e. Techniques of algometry--(1) Biologic methods. Biologic methods have been used in laboratory studies to assess the effectiveness of analgesics. The Panel does not require such studies, but if they are available, they may assist in evaluation of the ingredient. For example, solutions of known concentrations of analgesics have been applied to the skin of the limbs of frogs (Ref. 11). The areas are tested with a physical or chemical stimulus of known intensity, and the motor responses are observed. In

one method, a paper disk impregnated with a known concentration and volume of acetic acid is applied to the skin, and the effect upon the withdrawal of the extremity is observed. Other amphibia and reptiles have been immersed in solutions of anesthetic or analgesic agents, and the responses to reflex stimulation have been observed and quantitated. The skin of the frog, however, is vastly different from that of humans and other mammals, both in histologic structure and absorptive capacity. Therefore, these data cannot be extrapolated to humans and are only supportive.

The cornea of the rabbit or guinea pig likewise is often used as a test site for topical anesthetics. The disappearance of the blink reflex in the eye after application of a stimulus of known intensity yields data that are considered to be objective. Tests on the cornea of animals, again, are by themselves not meaningful because the surface of the cornea cannot be likened to human skin. Such data are merely supportive and must be accompanied by data on humans.

(2) Methods used in humans. Pain may be superficial or deep. It may be elicited by thermal, mechanical, electrical, or chemical stimuli. The impulses that incite

cutaneous pain and itch are carried by the same fibers and can be reproduced by varying the intensity of a stimulus. Therefore, the methods described below are useful for studying both pain and itch.

(i) Stimulation using radiant heat. Some investigators have used the Hardy-Woolf-Goodell pain threshold apparatus as a source of painful stimuli (Refs. 12 and 13). The apparatus described in the literature consisted of a calibrated radiometer that provided a thermal stimulus to the skin. The source of energy was a 1,000-watt incandescent lamp, a condensing lens that permits the rays to be focused on the areas to be tested, and a rheostat to vary the intensity of the beam. Test areas approximately 3.5 cm in diameter were blackened with some form of finely pulverized purified carbon, such as carbon black or a suspension of India ink. This insured complete absorption and conversion of the radiant energy to heat and prevented penetration of the rays below the surface of the skin. The effects of pigmentation of the skin were also eliminated. The subject verbally reported what sensation was experienced at the end of a particular interval of time. Usually a 3-second exposure with a standard beam intensity was necessary to evoke a sensation

of pricking, pain, itching, or burning and was considered to be the least perceptible stimulus, and therefore, the pain threshold.

In using this method, results are best obtained by approaching the pain threshold by using two or three subminimal stimuli. Thus, overstimulation of a test area is avoided. Such overstimulation may cause subsequent hypalgesia (decrease in the sensation of pain), which could alter the absorption of the agents being tested due to injury of the skin, even though the skin remains intact. The blackened areas are coated with the preparations to be studied, including one which contains only the medium used for incorporating the active ingredients. This, therefore, serves as a control. The subjects should be unaware of the composition of preparations applied to a particular area. Sensations of warmth or coolness, if they are caused by one of the ingredients, may prevent the test from being completely blind because they may stimulate sensory receptors other than those of pain. The subject is, therefore, able to identify the preparation on reapplication or retesting and to distinguish it from other preparations and the control. Blind studies may be performed only if neither the subject nor the individual

interpreting the responses to the stimuli knows the nature of the preparation that has been applied over the test area. The material may be applied by a third person who knows its identity or it may be coded so that no one knows its identity. The code is broken after the tests are complete. Thus, such an experiment can be considered blind, particularly if none of the ingredients evokes sensations other than analgesic or antipruritic. Enough data should be obtained for statistical analysis.

The objection to this technique is that the thermal stimulus may elicit a response from receptors subserving warmth, rather than those subserving pain and itch. Furthermore, the application of carbon black and the heat from the radiant energy may change the water content of the skin, and thereby alter its absorptive capacity during the experiments.

(ii) Method using pricking as a stimulus. Monash (Ref. 14) devised several topical analgesic testing methods that permit the continuous application of a test solution. The testing was done by pricking with a sharp instrument. A ball of absorbent cotton approximately 1 cm in diameter soaked with the desired solution was placed

on the skin and covered with waxed paper or cellophane and then fixed in place with adhesive plaster. Thirty minutes later the cotton was removed and the area pricked with a sharp instrument to determine whether anesthesia was present. If not present, the cotton was then again soaked with the solution and reapplied. The testing was performed at 15-minute intervals. When anesthesia was complete, the patch was removed and the duration of anesthesia determined by subsequent testing at 15- to 30-minute intervals.

The chief objection to this technique is that the agents are not ordinarily applied to the skin in this manner. Furthermore, it is difficult to quantitate the intensity of the stimulus by merely pricking the surface, unless the study is designed to observe only the anesthetic effect, and not the analgesic effect, of a preparation. The method tests for anesthesia, partial or complete blockade, or hypalgesia, but does not test for analgesia in cases where relief of burning or itching is obtained without the patient experiencing numbness. Pricking does not evoke a sensation of itch, because itch is evoked by subminimal stimulus while the nerve endings still remain partially active and are able to perceive

pain. However, this method is useful in determining whether percutaneous absorption of topical anesthetic bases and salts occurs.

(iii) Electrical stimulation. Electric currents have been used to evoke the sensation of pain and itching on the skin. Hardy et al. (Ref. 12) note that the first recorded use was that by Macht et al. in 1916, who applied faradic current to the scrubbed skin of the dorsum of the hand and determined the increase in the pain threshold after the application of cocaine and certain opium alkaloids.

Dalili and Adriani (Refs. 10 and 15) have recently devised a method utilizing a pulsatile alternating current delivered from a Grass 44 Model stimulator that selectively activates the receptors in the cutaneous nerves that subserve pain and itch. A subminimal stimulus evokes a sensation of itching and burning (Ref. 16). Increasing the intensity of the stimulus induces pain. Further increases cause the current to penetrate the subcutaneous structures and stimulate the motor fibers, producing muscle contraction, twitching, and cramping. A pulsatile current consisting of sine waves of 30 cycles per second of 5 milliseconds duration with 2-millisecond periods of

silence between impulses is used. Repeated stimulation reproduces a sensation of itching and pricking without apparent injury to the cutaneous structures. A pinpoint metal tip is necessary as the exploring electrode. The type of electrode used is important because current density becomes a factor. The minimal quantity of current that, when localized over a small area of pinpoint size, is effective in causing a stimulus fails to evoke a response when applied over a wider area. From 25 to 40 volts are generally necessary to deliver the required amperage. This is due to the variation of the resistance of the skin in different subjects. The resistance of the skin varies from subject to subject and even in the same subject at different times. The threshold of excitation may be reduced to 0.3 milliampere by pinpointing the contact area with the fine tip of the electrode. The necessary amperage varies from subject to subject, ranging from 1 to 10 milliamperes, but remains constant for each subject and for the same subject in each period of testing.

Adriani and Dalili (Ref. 10), as well as the investigators using the thermal stimulation technique described above, selected the volar surface of the forearm as the

test site. An indifferent electrode is fixed to the dorsum of the forearm over gauze soaked in saline. Control values are established at multiple points over the test site, which measures from 5 to 7.5 cm^2. The preparation under investigation is applied for 30 minutes. Areas 1 x 1 cm are wiped dry at 15-minute intervals and stimulated for 1- to 2-second intervals until itching is perceived. Generally 1 hour elapses before the entire area is wiped and tested. A single application for 60 minutes established the clinical usefulness of a preparation. As is the case with other workers, test sites coated with a placebo are used as controls. One possible objection to this method is that a stimulus greater than is necessary to cause itch may be applied, causing tingling, which may be misinterpreted by some subjects.

Adriani and Dalili (Ref. 10) produced ultraviolet light burns using a GE Model 1F2 lamp held 60 cm from the volar surface of the forearm for 8 to 18 minutes and tested the effectiveness of various agents in relieving the discomfort. Patients not complaining of itching and burning after developing erythema and not experiencing hypersensitivity to touch were excluded from study.

Obviously, data obtained in such a study are subjective because reliance must be placed upon the patient's interpretation of the degree of relief obtained. A xenon lamp may be used to provide radiation of known and fixed wavelengths, as would be the case in evaluating sunscreens, but is not necessary. Thus, studies could be simultaneously performed on both the injured intact skin and the intact skin. Efficacy is determined subjectively by questioning the subject on the degree of relief of the ensuing discomfort. Responses to electrical stimulation are graded 0 if no relief of discomfort resulted, 1+ if a partial block is obtained, or 2+ if no itching or burning occurs from the electrical stimulation. Painful tingling or vibratory sensations result if the current is increased beyond the control value or if the intensity of the current is increased when a blockade is obtained. These workers also noted that in some cases subjects complained that an aggravation of discomfort resulted after application of the preparation. This increase in discomfort has been termed "antianalgesia." Tests of such a response were recorded and coded as E. In addition, the subject's evaluation of the relief of discomfort on the injured skin was graded as 0 if no relief of symptoms resulted, 1+ if

the relief was partial, and 2+ if there was complete relief of itching, pricking, and burning (Ref. 15).

(iv) Using intradermal wheals as test sites. Adriani and Dalili (Refs. 10 and 15) also infiltrated successive strata of the epidermis with 0.01 to 0.02 mL of a soluble topical anesthetic with the 30-gauge needle of a tuberculin syringe. Stimulation over the treated area with the electric current no longer caused itching and burning. Increasing the amperage and voltage elicited vibratory and tingling sensations, indicating that the current acted on receptors of different types. The nerves in the deeper layers of the skin and muscle apparently were not blocked and were stimulated.

Data in which studies have been performed using an intradermal wheal are of no value in support of a submission that makes claims for therapeutic effectiveness of a particular ingredient when applied topically to the intact skin. An ingredient applied in this manner is introduced beneath the stratum corneum into the stratum germinativum, where it is readily bioavailable and comes into contact with the nerve endings in the skin and produces anesthesia. Some investigators have used such

data to support claims for effectiveness of topically applied preparations. The area over the wheal is not responsive to pricking or other forms of stimulation because complete anesthesia ensues.

(v) Additional methods for inducing experimental pain. It has been indicated above that induced pain differs from pathologic pain due to trauma or disease (Ref. 14). Tests of the effectiveness of analgesics in the laboratory using experimentally induced pain may not coincide with the results obtained when pain is of pathologic origin. Fortunately, the situation is different as far as the skin is concerned, because pain of pathologic origin can be produced by thermal injury or by abrading the skin.

Burning with ultraviolet light has been described above in the section on electrical stimulation. Adriani and Dalili (Ref. 10) used a template which has six openings to permit specific areas to be exposed to ultraviolet radiation to cause a burn on the forearm. This results in six areas for use as test sites. At least five ingredients and a placebo may be used simultaneously. If both arms are used, this permits the testing of 10 preparations, or a cross-over technique, if so desired.

Although many techniques are available for producing abrasions and disrupting the skin for investigational purposes, the most popular, the least traumatic, and most commonly used method is that in which sticky tape is used for excoriation of the skin. The tape is applied over the desired area and removed 10 to 15 times in succession. In the process, the epidermis is disrupted and the stratum corneum is removed, thereby breaking the integrity of the epithelial barrier. Burning sensations can be elicited by application of dilute alcohol or citric or acetic acid solutions to the abraded area, after which the analgesic is applied.

Another method that has been used for causing very fine abrasions of the skin is to apply cowhage (itch powder) to an area of the skin. Cowhage is derived from a tropical woody vine covered with barbed hairs that, when applied to the skin, cause intense itching. Tests using cowhage are valid if the experiment is designed to test the effectiveness of a preparation on the damaged skin, but not on the intact skin. The fact that the agents are absorbed easily following such treatment and exert a topical anesthetic or hypalgesic effect must be recognized. They are not acting through intact skin.

(vi) Abrading the skin. Vigorous scrubbing with a brush may also be used as a method of abrading the skin. Abrasions may be obtained by rubbing the skin with a fine grade of sandpaper or other abrasive material. These techniques are not only less acceptable to volunteers than stripping, but are also less controllable.

Application of an ingredient that is only analgesic on the intact skin may produce total anesthesia on the damaged or abraded skin (Ref. 12). This can be easily tested by pinpricking, radiant heat, electric current, or application of chemicals that cause stinging but no injury. In some cases the agent is not sufficiently potent, and partial anesthesia or, more accurately, hypalgesia is obtained. Testing on abraded skin is considerably less subjective than methods for testing the effects of drugs on the intact skin.

(3) Selection of test sites. The thickness of the skin is an important consideration in conducting investigations of topical anesthetics and analgesics. Thickness of all layers varies from one area of the body to another. The epidermis, particularly the stratum corneum, is thickest in the soles and the palms (Ref. 9). Penetration and absorption are poorest at these sites

because the outer, horny keratin layer is dense in these areas and the stratum lucidum, which is thin in other areas of the body, is well defined beneath the stratum corneum. In most cases, investigators have used the volar surface of the forearm as the most convenient site for testing. This area is most amenable for the quantitation of the degree of analgesia and anesthesia. The thickness of skin in the volar surface appears to be less than it is in most areas of the body (Ref. 9). And because the number of hair follicles and sebaceous glands in this area is sparse compared with other areas of the body, any absorption or penetration that occurs via the hair follicles and other appendages in the skin is reduced. Most investigators doubt that the therapeutic effects obtained from these ingredients are due to absorption along the hair follicles and from the sebaceous glands. Ample evidence exists that absorption occurs directly through the stratum corneum (Ref. 9).

The selection of the test site area is important because the number of terminal nerve endings per cm^2 of skin varies from one area of the body to another. Meaningful data may not be obtained if an area of low pain sensitivity is selected.

Mucocutaneous junctions as test sites: Studies performed at test sites utilizing mucocutaneous junctions are not acceptable for obtaining data on the skin alone because preparations that are readily absorbed and effective on the mucous membranes are not necessarily absorbed and effective on the skin. Data obtained by applying analgesics and anesthetics at the lips, nares, anorectal areas, and the female genitalia are not suitable except in instances where the product is intended to be applied to these areas (Refs. 10 and 15).

(4) Use of other or new techniques. The Panel recognizes that there is a dearth of methods for determining the analgesic effects on the skin and that other methods may be developed in the future. The determination of the degree of penetration of a radioactive ingredient into the skin has been suggested as one possible technique. However, the fact that a drug penetrates the skin does not necessarily mean that it is effective as a topical analgesic. It is doubtful that this technique will yield data of value. Systemically administered drugs that produce itching could be used but are not practical at this time. Morphine exerts such an effect. Morphine, however, is not the agent of choice, nor does it produce

itching in all subjects to whom it is given. Morphine apparently acts peripherally to reduce the threshold for itch, even though centrally it elevates the threshold for pain. The analgesic effect may counterbalance the pruritic effect, and no sensation of itch may result. Methods utilizing pressure or ischemia are suitable for evaluating deep pain but not cutaneous pain. Although other methods and techniques are available for use in evaluating pain, they are too detailed to discuss in this document.

6. Evaluation of counterirritants and claims for deep-seated pain. a. Introduction. The methods described above are intended to evaluate anesthetics, antipruritics, and drugs that produce analgesia by depressing cutaneous sensory receptors, and are not applicable in evaluating the effectiveness of analgesics that stimulate cutaneous sensory receptors and exert their effects by counterirritation. The Panel recognizes that methods are not available for experimentally inducing pain of the type relieved by counterirritants. Investigators cannot rely upon normal subjects to obtain data to evaluate effectiveness. The Panel, therefore, recommends that studies be performed on patients with pathologic pain

with well-defined discomfort involving the musculoskeletal system, such as arthritis, tendonitis, bursitis, myositis (traumatic or otherwise), neuritis, strains, sprains, related syndromes, or deep-seated pain. The general comments on the selection and treatment of subjects for study, the evaluation of data, the establishment of dose-effect relationships, labeling, etc. are also applicable to drugs acting by counterirritation. Studies on patients are to be conducted as described below.

If possible, studies should be double-blind. Patients who have similar types of disorders should be randomly selected for treatment, divided into two groups, and the groups compared. One group is treated with the drug being tested and another group with the vehicle alone, suitably controlled. The disease process for which the testing is done should have the same etiology. For example, when tests are performed on patients with arthritis, all patients should have the same type of arthritis, i.e., rheumatoid, osteoarthritis, etc. The cross-over technique may be used when the condition under study is chronic and only temporary symptomatic relief is obtained by application of the medicament. The cross-over technique is not

suitable in subjects who experience partial improvement of symptoms after application of a medicament or in self-limiting conditions. A minimum of 25 subjects should be tested with the drug and 25 with the suitable vehicle for each type of syndrome by two independent investigators in single sequence methodology. In cross-over studies, 25 subjects altogether are sufficient. The effects could be evaluated on at least two types of painful disorders, e.g., arthritis, bursitis, myositis, tenontitis, and traumatic injuries. The mode of application of the drug must be specified and should be uniform in a particular clinical trial. The data on testing should include application frequency, as specified in the labeling, for not less than a 48-hour period. A washout period of at least 12 hours should be used in cross-over studies (Ref. 2).

b. Methods of evaluation. The following subjective and objective methods of evaluation are available to determine the effectiveness of analgesics that act by counterirritation:

(1) Evaluation of the effects on pain. Certain musculoskeletal disorders are accompanied by inflammation that causes swelling, tenderness, and redness, as well as

pain. A description of the type of pain relief should be recorded and the degree of relief based upon an applicable scoring system, as for example, 0 = none, 1 = slight, 2 = moderate, and 3 = complete. The scores should be evaluated statistically and values compared with those obtained from treatment with a placebo vehicle control. The Panel recognizes that the inflammatory process may not recede, but the preparation may cause varying degrees of pain relief and such data is acceptable (Refs. 13 and 17).

The presence of erythema and its intensity, and the appearance of edema (indurated, pitting, or soft) may be parameters that could be objectively evaluated and correlated with the degree of relief of pain and changes mentioned above.

(2) Effects on range of motion of joints. The range of motion in degrees should be determined using a protractor or other device acceptable for mensuration of angles. Pretreatment values should be established for both active and passive movement and changes in the degree of extension, flexion, adduction, or abduction of a limb. This data should be accompanied by a description of the type and intensity of pain and degree of pain relief during each maneuver before and after treatment. The

degree of pain should be rated on an acceptable scoring system as described above.

Measurements of the effect of the medication on motion should be made at sufficiently frequent intervals to determine the onset of analgesic effect, duration, degree of pain relief, and time of return of symptoms. Measurements should be objectively made. The technique of measurement should be consistent throughout the study and made by the same observer throughout a trial period. The Panel recognizes that counterirritant analgesics are not curative and may cause no improvement in mobility of the joints or limbs but may still relieve pain and provide comfort as long as there is no attempt to move a limb or an extremity. Subjective data on pain relief are acceptable. The Panel also recognizes that although motion may not be restricted, pain will be elicited when a muscle or joint is activated voluntarily or moved passively, and that a topically applied medication may relieve such pain on movement of an extremity or a limb. In these instances, subjective data will be accepted by the Panel.

(3) Effects of pressure or palpation on musculoskeletal pain. Pain can be induced by using an

inflatable cuff that exerts pressure on a metal or plastic plate over the affected area. The pressure in the cuff is measured by a manometer. The amount of pressure necessary to inflate the cuff to elicit pain is an indicator of the relief obtained. The degree of pain should be based upon subjective response conceptions (Ref. 18). Pretreatment readings are established, and the variations in pressure noted at necessary intervals established by the observer. Pressure induced by adding a series of weights or applying pressure with a loaded spring could also be used.

(4) Relief of muscle spasm. Hypertonus or muscle spasm accompanies musculoskeletal disorders to protect an affected part by splinting. Changes in muscle tone may be detected by use of the electromyograph. Pretreatment electromyographic values followed by measurements at appropriate time intervals may be instituted to determine the relief of spasm. If such studies are undertaken, these should be correlated with the degree of range of motion and the subjective evaluation of degree of pain relief mentioned above (Refs. 19 and 20).

(5) Measurement of skin temperatures. Topical analgesics which stimulate cutaneous receptors, send

impulses into central receptors that excite centers that control the caliber of the blood vessels and reflexly cause vasodilation. An increase in blood flow results over the area of application of the medicament and in the vessels in the skin area subserved by the spinal segment receiving these cutaneous impulses. An increase in skin temperature results, which can be detected by using a thermocouple, thermistor, or other device that detects changes in skin temperature. An increase in skin temperature is not proof of efficacy but does provide confirmatory evidence with other data obtained and the subjective responses of the patient that a drug is exerting a pharmacologic effect.

(6) Blood plasma levels. Certain analgesics with counterirritant effects may be absorbed percutaneously and disseminated to the tissues, where they may exert an anti-inflammatory effect that is presumed to produce analgesia. Other effects may be produced. The Panel could accept data to support effectiveness of an ingredient as a topical analgesic if the action is systemic and not topical in the skin.

Method (1) or (2) or (3) discussed above is mandatory and must be used in the evaluation of the effectiveness of

an ingredient. Methods (4), (5), or (6) are optional methods that may be used in support of the results obtained from any one of the above tests.

7. Summary outline of required testing. The following outline summarizes the tests required to reclassify a Category III active ingredient to Category I status:

a. Studies required to demonstrate safety. The following studies are required to reclassify external analgesic active ingredients classified as Category III for safety considerations:

(1) Preclinical studies. The required preclinical studies have been discussed in detail elsewhere in this document. (See part III. paragraph C.4.a. above--Recommended toxicological studies.)

(i) Animal toxicity studies.

(ii) Skin irritancy, dermal toxicity, and photo-toxicity and photosensitization studies in animals.

(2) Clinical studies. Irritancy and sensitization studies in humans, utilizing the patch tests, are required.

b. Studies required to demonstrate effectiveness. (1) The following clinical studies are required to

reclassify all topical analgesic, anesthetic, and antipruritic active ingredients classified as Category III for effectiveness:

(i) When possible, one double-blind study on a minimum of 25 normal human subjects (volunteers) demonstrating topical analgesic effects of the final formulated product using one or more of the algesimetric methods discussed above. The test sites should be those areas of the skin known to be richly endowed with terminal pain-perceiving nerve endings.

(ii) When possible, one double-blind study on a minimum of 25 subjects with pathologic cutaneous lesions that cause pain, burning, or itch. The dose-response relationship should be established indicating the range between the minimum effective dose and the maximum safe dose. Where applicable, a comparison between the effects on the intact skin and the effects on damaged skin should be included in the study. The study should be done using the final formulated product and a placebo.

(iii) Where using the studies described above is not applicable, as with active ingredients that act by exerting an anti-inflammatory effect, when possible, double-blind studies should be done in a minimum of 25

subjects with edema or inflammatory disturbances of the skin that are as similar as possible and are at approximately the identical test site in all subjects. The studies should be done using the final formulated product and a suitable vehicle. The dose-response relationship should be established indicating the range between the minimum effective dose and the maximum safe dose. Where applicable, a comparison between the effects on the intact skin and the effects on damaged skin should be included in the study.

(2) The following clinical studies are required to reclassify all topical counterirritant active ingredients classified as Category III for effectiveness: When possible, double-blind studies on a minimum of 25 subjects using the ingredient and a suitable vehicle for a control for 2 different types of painful disorders and evaluation with methods (1), (2), or (3) described above. Tests should be performed by two independent investigators for each of the painful disorders studied.

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The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 348, to read as follows:

PART 348--EXTERNAL ANALGESIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A--General Provisions

Sec.

348.1 Scope.

348.3 Definitions.

Subpart B--Active Ingredients

348.10 External analgesic active ingredients.

348.20 Combinations of external analgesic active ingredients.

Subpart C--[Reserved]

Subpart D--Labeling

348.50 Labeling of external analgesic products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A--General Provisions

§ 348.1 Scope.

An over-the-counter external analgesic product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 348 and each of the general conditions established in § 330.1 of this chapter.

§ 348.3 Definitions.

(a) Age. Infant (under 2 years of age), child (2 to under 12 years of age), and adult (12 years of age and over).

(b) Cutaneous sensory receptor. A sense organ that is connected to the terminal fibers of a network of nerves in the skin for the perception of pain, itching, cold, warmth, touch, and pressure.

(c) External analgesic. A topically applied drug that has a topical analgesic, anesthetic, or antipruritic effect by depressing cutaneous sensory receptors, or that

has a topical counterirritant effect by stimulating cutaneous sensory receptors.

(d) Topical analgesic. An externally (topically) applied drug that, by depressing cutaneous sensory receptors, relieves pain without necessarily abolishing other sensations, or that causes partial blockades of subcutaneous terminal nerve endings so that a minimal stimulus evokes no painful response, but a greater stimulus does.

(e) Topical anesthetic. An externally (topically) applied drug that completely blocks pain receptors, resulting in a sensation of numbness and an abolition of responses to painful stimuli by depressing cutaneous sensory receptors.

(f) Topical antipruritic. An externally (topically) applied drug that relieves itching by depressing cutaneous sensory receptors.

(g) Topical counterirritant. An externally (topically) applied drug that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints, or viscera distal to the site of application by stimulating cutaneous sensory receptors.

Subpart B--Active Ingredients

§ 348.10 External analgesic active ingredients.

The external analgesic active ingredients of the product consist of the ingredients identified below, within the concentrations established.

(a) External analgesic active ingredients that stimulate cutaneous sensory receptors (counterirritants).

(1) Allyl isothiocyanate 0.5 to 5.0 percent.

(2) Ammonia water, stronger 1.0 to 2.5 percent.

(3) Camphor exceeding 3.0 percent up to 11 percent.

(4) Capsaicin 0.025 to 0.25 percent (or the equivalent amount of capsaicin in capsicum or capsicum oleoresin).

(5) Histamine dihydrochloride 0.025 to 0.10 percent.

(6) Menthol exceeding 1.25 percent up to 16 percent.

(7) Methyl nicotinate 0.25 to 1.0 percent.

(8) Methyl salicylate 10 to 60 percent.

(9) Turpentine oil 6 to 50 percent.

(b) External analgesic active ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics. (1) Benzocaine 5 to 20 percent.

(2) Benzyl alcohol 10 to 33 percent.

(3) Butamben picrate 1 percent.

(4) Camphor 0.1 to 3.0 percent.

(5) Dibucaine 0.25 to 1.0 percent.

(6) Dibucaine hydrochloride 0.25 to 1.0 percent.

(7) Dimethisoquin hydrochloride 0.3 to 0.5 percent.

(8) Diphenhydramine hydrochloride 1 to 2 percent.

(9) Dyclonine hydrochloride 0.5 to 1.0 percent.

(10) Hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) 0.25 to 0.5 percent.

(11) Juniper tar 1 to 5 percent.

(12) Lidocaine 0.5 to 4 percent.

(13) Lidocaine hydrochloride 0.5 to 4 percent.

(14) Menthol 0.1 to 1.0 percent.

(15) Methapyrilene hydrochloride 1 to 2 percent.

(16) Phenol 0.5 to 2.0 percent.

(17) Phenolate sodium 0.5 to 2.0 percent.

(18) Pramoxine hydrochloride 0.5 to 1.0 percent.

(19) Resorcinol 0.5 to 3.0 percent.

(20) Tetracaine 1 to 2 percent.

(21) Tetracaine hydrochloride 1 to 2 percent.

(22) Tripelennamine hydrochloride 0.5 to 2.0 percent.

§ 348.20 Combinations of external analgesic active ingredients.

(a) Combinations of external analgesic active ingredients that stimulate cutaneous sensory receptors (counterirritants). (1) The active ingredients of the combination product consist of no more than one active ingredient from each of any two, three, or four of the following groups of counterirritant active ingredients when used within the concentrations identified in § 348.10(a):

(i) Allyl isothiocyanate, ammonia water, methyl salicylate, or turpentine oil.

(ii) Camphor or menthol.

(iii) Histamine dihydrochloride or methyl nicotinate.

(iv) Capsaicin, capsicum, or capsicum oleoresin.

(2) The active ingredients of the combination product consist of no more than one active ingredient from each of any one, two, or three of the counterirritant groups identified in paragraph (a)(1)(i), (iii), or (iv) of this section, and camphor and menthol when used within the

topical concentration limits identified in § 348.10(a).

(b) Combinations of external analgesic active ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics). (1) The active ingredients of the combination product consist of no more than one single active ingredient from each of the following two groups of analgesic, anesthetic, and antipruritic active ingredients within the concentrations identified in § 348.10(b):

(i) Benzocaine, butamben picrate, dibucaine, dibucaine hydrochloride, dimethisoquin hydrochloride, dyclonine hydrochloride, lidocaine, lidocaine hydrochloride, pramoxine hydrochloride, tetracaine, or tetracaine hydrochloride.

(ii) Benzyl alcohol, camphor, juniper tar, menthol, phenol, resorcinol, phenolate sodium, or thymol.

(2) The active ingredients of the combination product consist of any single active ingredient identified in paragraph (b)(1)(ii) of this section, and any single active ingredient in the following group of analgesic, anesthetic, and antipruritic active ingredients: diphenhydramine hydrochloride, methapyrilene hydrochloride, or tripelennamine hydrochloride.

(3) The active ingredients of the combination product consist of any single active ingredient identified in paragraph (b)(1)(ii) of this section, and camphor and menthol.

(c) Combinations of external analgesic active ingredients with other externally applied active ingredients. (1) The active ingredients of the combination product consist of any single active ingredient identified in either paragraph (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this section, and any generally recognized safe and effective skin protectant active ingredient or skin protectant combination of ingredients, provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations, and for the temporary protection and lubrication of minor skin irritations."

(2) The active ingredients of the combination product consist of any single active ingredient identified in either (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this

section, and any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination, provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations, and for protection against wound contamination."

Subpart C--[Reserved]

Subpart D--Labeling

§ 348.50 Labeling of external analgesic products.

(a) Statement of identity. The labeling of the product contains the established name of the drug(s) identified under § 348.10 and identifies the product as follows:

(1) For products containing any external analgesic active ingredients identified in § 348.10 other than hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) identified in § 348.10(b)(10): the labeling identifies the product as an "external analgesic."

(2) For products containing external analgesic products active ingredients identified in § 348.10(b)(10): the labeling identifies the product as an "antipruritic."

(b) Indications. The labeling of the product contains a statement of the indications under the heading "Indication(s)" that is limited to the following phrases:

(1) For products containing any external analgesic active ingredients identified in § 348.10(a): "For the temporary relief of minor aches and pains of muscles and joints, such as simple backache, lumbago, arthritis, neuralgia, strains, bruises, and sprains."

(2) For products containing any external analgesic active ingredients identified in § 348.10(b) other than hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) identified in § 348.10(b)(10): "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations."

(3) For products containing external analgesic active ingredients identified in § 348.10(b)(10): "For the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison

ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

(c) Warnings. The labeling of the product contains the following warnings under the heading "Warnings":

(1) For products containing any external analgesic active ingredient identified in § 348.10(a) and (b):

(i) "For external use only."

(ii) "Avoid contact with the eyes."

(iii) "If condition worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician."

(iv) "Do not use on children under 2 years of age except under the advice and supervision of a physician."

(2) For products containing any external analgesic active ingredient identified in § 348.10(a):

(i) "Do not apply to wounds or damaged skin."

(ii) "Do not bandage."

(3) For products containing butamben picrate identified in § 348.10(b)(3):

(i) "Do not use over extensive areas of the body."

(ii) "This product stains the skin and tissues, clothing, and other objects yellow."

(4) For products containing any external analgesic active ingredient identified in § 348.10(b)(5), (6), (12), (13), (20), and (21): "Do not use in large quantities, particularly over raw surfaces or blistered areas."

(5) For products containing phenol identified in § 348.10(b)(16): "Do not apply this product to extensive areas of the body or under compresses or bandages."

(6) For products containing resorcinol identified in § 348.10 (b)(18): "Do not apply this product to large areas of the body."

(d) Directions for use. The labeling of the product contains the following statement under the heading "Directions": For adults and children 2 years of age and older: Apply to affected area not more than 3 to 4 times daily. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a physician.

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before (insert date 90 days after date of publication in the FEDERAL REGISTER). Such comments

should be addressed to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before (insert date 120 days after date of publication in the FEDERAL REGISTER). Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: 11/19/79.

Nov. 19, 1979

Jere E. Goyan
Commissioner of Food and Drugs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL
Marcia Rosenberg